Attorney Docket No. 3477-112 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Jian-Ping Wu et al.
Application No.: 10/538,951
Filed: March 28, 2006
Title: *ACE INHIBITORY PEPTIDES FROM PLANT MATERIALS*

Confirmation No. 5581
Group Art Unit: 1654
Examiner: Maury A. Audet

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ALISTER D. MUIR
PURSUANT TO 37 C.F.R. § 1.132

Sir:

I, Alister D. Muir, do hereby declare and say as follows:

1. I am a named inventor on United States Application No. 10/538,951 and of the subject matter claimed therein.

2. I have a Ph.D. degree from the University of Canterbury, Christchurch, New Zealand. I am currently a Senior Research Scientist in BioProducts and Processing at the Saskatoon Research Centre, Agriculture & Agri-Food Canada. I have been conducting research in the area of natural products chemistry and the isolation and purification of bioactives from plants for 30 years and have authored or co-authored more than 55 publications related to these areas.

3. I have read and understood the Office Action mailed on November 28, 2007 and references cited in the Office Action.

4. The Office Action states that claims 1, 3-7, 10-11, and 14-16 are rejected as being unpatentable over Wu et al. in view of Garrison et al. and Eto et al.

Specifically, the Office Action states that these claims are not patentable because "[i]t would have been obvious at the time of the invention to arrive at the sequential steps for preparing an angiotensin converting enzyme (ACE) inhibitory peptide-containing hydrolysate in Wu et al., based on the advantageous teachings of Garrison et al...." The Office Action further states that the skilled artisan would have been motivated to combine the teachings of Wu et al. as to the use of proteolytic enzymes (e.g. Alcalase) to prepare ACE inhibitory peptide-containing hydrolysates with the teachings of Garrison et al. as to the steps of defatting the soy meal, using a solvent therein, and arrive at the presently claimed sequential three-step process of carrying out the same.

Firstly, I disagree that the teachings of Garrison et al. are advantageous. The Office Action describes the teachings of Garrison et al. as defatting the soy meal. Soy meal is by definition a defatted soy flake where the defatting solvent is a non-polar solvent such as hexane. Garrison et al. does not teach or indicate any advantage of further extraction of a defatted meal with a polar solvent in the preparation of a soy protein isolate. Garrison et al. isolates a protein fraction from the seeds that consists of specialized storage protein. Further, the process of Garrison et al. results in the isolation of only 60% to 90% of the protein from the seeds, thus omitting 10% to 40% of the other proteins (that are not within the protein granule fraction) (Garrison et al., col. 8, lines 15-20). In contrast, this 10% to 40% would be available for hydrolysis by a proteolytic enzyme in the presently claimed method.

Furthermore, the process of Garrison et al. is unnecessarily cumbersome in the context of the presently claimed invention. Garrison et al. is directed to isolating pure, undenatured protein to be used as a source of supplemental dietary protein. As such, these additional protein purification steps, and care to avoid degrading the protein, are important in that context. However, in the context of the presently claimed invention, the protein is *intended* to be cleaved, degraded, and denatured by the proteolytic enzymes. It is the *activity* of these resulting peptides that is important, not the *purity*, or even the quantity of protein. Therefore, adding in extra steps to purify a specialized portion of the protein within a seed is not an advantage a research technician would consider with regard to being motivated to produce the claimed invention. Instead, the present invention has the unobvious advantage of *not requiring purified protein.*

Indeed, increasing the recovery of unhydrolyzed protein would be counter productive as it would dilute the ACE inhibitory activity.

Secondly, considering that the process of Garrison et al. is cumbersome compared to that of the present invention, as well as the fact that up to 40% of the cellular protein (perhaps containing very active ACE inhibitory peptides) would be lost through the Garrison et al. process, a technician trying to produce ACE inhibitory peptides would not consider combining the teachings of Garrison et al. with that of Wu et al.

Thirdly, I further disagree that Wu et al. and Garrison et al. can be combined to provide the presently claimed invention. In fact, I believe that the Examiner has misinterpreted Garrison et al. and is additionally confusing "protein granules" with "seed meal or flour". As described above, protein granules are not the equivalent of seed meal or flour.

In summary, the process of Garrison et al. provides the following steps:

crush vegetable seeds;

suspend these oil-containing seeds in an aqueous solution containing a carbohydrate so as to isolate the protein granules and the oil from the remainder of the seed material;

defat the protein granules by contact with hexane; and

wash the protein granules with a water-alcohol solution to remove any remaining components of the aqueous solution.

In contrast, Wu et al. simply treats oil-free seed meal with Alcalase (a proteolytic enzyme).

These two teachings, when combined, *do not teach* our claimed process, wherein we:

contact oil-free impure crushed seeds or flour (there is *no step* in the process of Garrison et al. that uses oil-free crushed seeds or flour) with an organic solvent so as to provide peptides with increased ACE inhibitory activity;

separate the oil-free crushed seeds or flour from the organic solvent; and

treat the oil-free crushed seeds or flour with a proteolytic enzyme.

The inclusion of Eto et al., which merely teaches that the ACE inhibitory peptide Phe-Leu can be obtained from whey protein, does not provide any additional information over Wu et al. and Garrison et al. that would lead one to the presently claimed invention.

4. Claims 1, 2, 8-9, 12-13, 17-18, 19, and 21 are rejected as being unpatentable over Wu et al. in view of Garrison et al. and Eto et al. In addition, claims 22-30 are rejected as being unpatentable over Wu et al. in view of Garrison et al. and Eto et al. and further in view of Tzen et al.

The Office Action states that the claimed invention is not patentable because "it would have been obvious to one of ordinary skill in the art at the time the invention was made to make adjustments to conventional working conditions as merely a matter of judicious selection and routine optimization for providing a means for the expected result of proteolytic cleavage of proteins in soy meal in Wu et al., based on the advantageous teachings/suggestions in Garrison et al. and Eto et al...."

I disagree that routine optimization of the process of Wu et al., based on the teachings of Garrison et al., would lead to the presently claimed invention. If a technician attempted proteolytic cleavage of the isolated protein granule fraction of Garrison et al., this would not produce the highly active ACE inhibitory peptides of the presently claimed invention. Instead, they would simply arrive at a solution of pure cleaved peptides. However, these protein hydrolysates would have *reduced* ACE inhibitory activity compared to those of Wu et al. at least for the reason that 10 40% of the total cellular protein would be absent, potentially including the ACE inhibitory peptide-containing moiety of the total cellular protein. A product produced according to the combination of Garrison et al and Wu et al. as suggested in the Office Action would contain a higher proportion of inactive large peptide chains that are resistant to proteolytic cleavage. In contrast, in the presently claimed invention, many of these larger fragments would not be solubilized and would remain with the meal.

The present invention uses the step of contacting the oil-free seed meal or flour with an organic solvent, a step which provides a very surprising and unobvious advantage over Wu et al.,

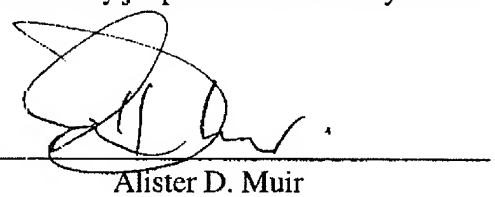
which is the production of ACE inhibitory peptides with enhanced activity. This step does not result in *more* ACE peptides, nor does it act to purify protein granules, as would be the goal to a technician reviewing Garrison et al.

Thus, the teachings of Garrison et al. are not advantageous over Wu et al. and a technician, knowing that it is important to retain all of the cellular protein so as to have the best chance at obtaining ACE inhibitory peptides, would not have been motivated to combine these teachings.

The inclusion of Eto et al., which merely teaches that the ACE inhibitory peptide Phe-Leu can be obtained from whey protein, and Tzen et al., which merely teaches that oil-containing seeds also contain protein, does not provide any additional information over Wu et al. and Garrison et al. that would lead one to the presently claimed invention.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 21st February 2008



Alister D. Muir